Remarks

Claims 1-3, 5-8, and 11-19 are pending in the application. Applicants have amended claim 1 above to specify that the live attenuated hepatitis A virus is prepared from the wild-type HAV strain L-A-I. Claim 6 has been similarly amended. In view of these amendments, claims 2, 13-15, 17, and 19 are canceled as unnecessary because the limitation of preparing the attenuated hepatitis A virus from strain L-A-I has been incorporated into independent claims 1 and 6. Upon entry of this amendment, claims 1, 3, 5-8, 11, 12, 16, and 18 will be pending before the Examiner.

Applicants respectfully traverse the §103 rejection set forth at pages 2-5 of the latest Office Action, as it would apply to the currently pending claims. Initially, Applicants note that claim 7 is directed to a stabilizer for lyophilized live virus, which comprises trehalose, ascorbic acid, urea, and inositol (in addition to other components), none of which are disclosed in a stabilizer by the cited references. Accordingly, claim 7 should be allowed. Each of the remaining rejected claims specifies wild-type HAV strain L-A-I as a part of the invention. As the Examiner correctly notes, none of the cited references teaches HAV strain L-A-I, and certainly none of the references provides a reasonable expectation of successfully producing a lyophilized live attenuated HAV vaccine using strain L-A-I. The primary references, Funkhouser *et al.* '110 and Funkhouser *et al.* '912, merely disclose live HAV variants modified from parental strain HM-175, and in particular the resultant modified virus 4380 which has imparted in it certain desired characteristics. However, as noted in column 13, lines 15-18 of the '110B1 patent, strain 4380 is over-attenuated, because it is not infectious. This characteristic reduces its efficiency when used in an attenuated vaccine, and in fact subsequent attempts by Funkhouser *et al.* have proven that they are unsuccessful in developing a live attenuated vaccine because their viral strains are either over-attenuated or have insufficient attenuation. In contrast, the subject invention involves methods and vaccines based on wild-type HAV strain L-A-I, which is surprisingly useful for making lyophilized live attenuated HAV vaccines. Approximately 3500 people were vaccinated with the claimed vaccine, then monitored and followed up for systemic and local side effects. The results of the clinical trials showed that more than 95% of overall anti-HAV seroconversion rates were achieved after one vaccination, and quantitative anti-HAV levels (Geometric Mean Titers, GMT) were about 4.438-4.464 at about 4th week after one vaccination, and about 5.098-6.276 at 8th week after one vaccination. The cited references fail to suggest that any particular strain could have such success, therefore, the claimed invention shows surprising results not suggested in the prior art.

In response to the Office Action's comments that the structural elements present in inactivated HAV and live HAV vaccines are the same, Applicants respectfully assert that a live HAV is different from inactivated virus in certain significant biological properties which affect its immugenicity. A live virus maintains its nucleic acid core in a protective protein or lipoprotein envelope which enables the live virus to maintain its possession of proliferative and infectious abilities. In contrast, inactivated virus has only a protein envelope by which its immugenicity is generated, but having no proliferative and infectious abilities, and thus having different immunological properties. For a live picornavirus, such as HAV, having a duplicatable nucleic acid core and without lipids in its outer envelope, there were no successful examples of lyophilization in the prior art. Applicants were the first to successfully produce a lyophilized live attenuated vaccine based on a picornavirus. Neither the primary nor the secondary references disclose successful lyophilization of a live attenuated HAV virus. At best, there might have been a suggestion to try to produce such a vaccine, but the references do not provide any reasonable expectation of success. To support an obviousness rejection, the law is clear that one must find both the suggestion, and the expectation of success, in the prior art. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Because of the surprising success Applicants have had with strain L-A-I, and because the prior art failed to provide any expectation of success using this strain, no *prima facie* case of obviousness has been set forth. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants gratefully acknowledge the indication at page 5 of the Office Action that claims 5, 8, 14, and 16-19 would be allowable if rewritten in independent form. Applicants belive that in view of the amendments, all pending claims are now in condition for allowance and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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JL/srp
Attachment: Petition and Fee for Extension of Time